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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/674,857	Applicant(s) ARMOUR ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-29 and 31-49* is/are pending in the application.

4a) Of the above claim(s) *16-29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 16-29, and 31-49 are pending.

2. Claims 16-29 and 31 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Applicant urges to reconsider the finality of the lack of unity in the election restriction requirement, filed 1/6/03, is acknowledged. The traversal is on the grounds that (1) there is no justification for lack of unity in the variable region. (2) The effector region of the binding molecule is the invention here. (3) Cole et al's V234 and A235 are IgG2 native and Cole et al have not been shown to bind FcRn and/or FcγRIIb. (4) The teachings of Greenwood et al are based on different technology, namely domain switching and had different aims than those of the present invention. (5) The present claims have now been limited to either 233P, 234V, 235A, and 236 G or no residue. This is not found persuasive because of the reasons set forth in the restriction mailed 6/28/01 and FAOM mailed 7/2/02. In contrast to Applicant's assertion that the lack of unity in the restriction requirement is based on the variable region, Greenwood *et al* teach a binding molecule such as chimeric recombinant antibodies DS1141, DS4414 comprising (i) a binding domain capable of binding a target molecule such as CAMPATH-1 antigen (CD52) and (ii) an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human immunoglobulin heavy chain wherein the reference binding molecule is capable of binding to the target molecule without significant complement mediated lysis or triggering cell mediated destruction of the target (ADCC) and the reference chimeric effector domain is derived from human immunoglobulin heavy chain CH2 domain from IgG1, and IgG4 (See Figs 1-4, in particular). Greenwood *et al* teach various amino acid substitution such as A at 325 (325A), G at 327 (327G), S at 330 and 331 (330S, and 331S) in the effector CH2 domain of human IgG1 or IgG 4. Mogan *et al* teach various amino acid substitution in the effector CH2 domain such as A at 325 in human IgG1. Chappel *et al* teach various amino acid substitution such as P at position 233, V at position 234 and A at position 235 in the effector CH2 domain of human immunoglobulin selected from the group such as IgG1, IgG2 and IgG4. Cole *et al* teach IgG2 variants having Ala at 234, Ala or Glu at 235, Gly or no residue at 236 and these residues are responsible for low affinity for FcγRI and FcγRII, and ineffective in mediating

cytotoxicity against target cells (See Table 1, page 3617, column 2, page 3620, column 1, in particular). From the combined teachings of Greenwood *et al,* Mogan *et al* Cole *et al* and Chappel *et al,* it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention. Further, the term "has" in amended claims 32 and 41 is open-ended. It expands CH2 domain to include additional amino acid substitutions to read on the teachings of Greenwood et al. In response to Applicant's argument that none of the references teach the desirability of balancing of these other functions (FcRn and/**or** FcγRIIb), it is noted that base claims 32 and 41 recite "FcRn and/**or** FcγRIIb". The examiner takes the position that it is meant to be FcRn and Fc; FcRn **or** FcγRIIb. In response to Applicant's argument that the teachings of Greenwood et al is based on different technology, a product is a product, irrespective how it is made. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention. Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention. Therefore, the requirement of Group II (now claims 32-49) and Groups III-XXI is still deemed proper and is therefore made FINAL.

4. In view of the amendment filed 1/6/03, the following objections and rejections remain.

5. The disclosure is objected to because SEQ ID NO is required for every sequence in Figure 17 in the Brief Description of Drawing. It is noted that amendment to the description of drawing filed 5/18/01 has indicated SEQ ID NO. However, the SEQ ID NOS for sequences other than G1Δab, G2Δa and G1Δac are not clear, especially for sequence G4Δc in Figure 17 as well as newly submitted claim 33.

6. The abstract of the disclosure is objected to because it is too long. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said,"

should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 32-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a binding molecule which is a recombinant human immunoglobulin comprising (i) a binding domain capable of binding to a target molecule wherein the binding domain is selected from the group consisting of RhD antigen (Fog-1) and CAMPATH-1 (CD52), (ii) an effector domain having an amino acid sequence substantially homologous to all or part of a constant domain of a human immunoglobulin heavy chain; wherein the binding molecule is capable of binding to the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target and capable of specifically binding to FcRn and/or FcγRIIb and wherein the effector domain is a chimeric domain which is derived from two or more human immunoglobulin heavy chain CH2 domains, which human immunoglobulins are selected from IgG1, IgG2 and IgG4, and wherein the chimeric domain is a human heavy chain CH2 domain consisting of the following blocks of amino acids at the stated positions: P at 233, V at 234, A at 235, G at 236, G at 327, S at 330 and S at 331, (2) the said binding molecule wherein the effector domain is selected from G1Δac of SEQ ID NO: 3 or G4Δc as shown in Figure 17 for inhibiting monocyte activation, complement mediated lysis of cell and ADCC in vitro, (3) the said binding molecule wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with the first or second human immunoglobulin heavy chain CH2 domain, (4) the said binding molecule wherein the effector domain has retained an affinity for FcγRIIb, (5) a preparation comprising said binding molecule plus a pharmaceutically acceptable carrier, (6) a binding molecule which is a recombinant human immunoglobulin comprising (i) a binding domain capable of binding to a target molecule wherein the binding domain is selected from the group consisting of RhD antigen

(Fog-1) and CAMPATH-1 (CD52), (ii) an effector domain having an amino acid sequence substantially homologous to all or part of a constant domain of a human immunoglobulin heavy chain; wherein the binding molecule is capable of binding to the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target and capable of specifically binding to FcRn and/or FcγRIIb and wherein the effector domain is a chimeric domain which is derived from two or more human immunoglobulin heavy chain CH2 domains, which human immunoglobulins are selected from IgG1, IgG2 and IgG4, and wherein the chimeric domain is a human heavy chain CH2 domain consisting of the following blocks of amino acids at the stated positions: P at 233, V at 234, A at 235, no residue at 236, G at 327, S at 330 and S at 331 and is at least 98 & identical to a CH2 sequence (residues 231-240) from human IgG1 or IgG2 having said modified amino acids, (7) the said binding molecule wherein the effector domain is selected from G1Δab of SEQ ID NO: 1 or G2Δa of SEQ ID NO: 2, (8) the said binding molecule wherein the effector domain is selected from G1Δab of SEQ ID NO: 1 or G2Δa of SEQ ID NO: 2 wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with *any* first or second human immunoglobulin heavy chain C_H2 domain, and retained an affinity for FcγRIIb and (9) a preparation comprising a binding molecule wherein the binding molecule which is a recombinant polypeptide comprising: (i) a binding domain capable of binding to a target molecule wherein the binding domain is selected from the group consisting of RhD antigen (Fog-1) and CAMPATH-1 (CD52), (ii) an effector domain having an amino acid sequence substantially homologous to all or part of a constant domain of a human immunoglobulin heavy chain; wherein the binding molecule is capable of binding to the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target and capable of specifically binding to FcRn and/or FcγRIIb and wherein the effector domain is a chimeric domain which is derived from two or more human immunoglobulin heavy chain CH2 domains, which human immunoglobulins are selected from IgG1, IgG2 and IgG4, and wherein the chimeric domain is a human heavy chain CH2 domain consisting of the following blocks of amino acids at the stated positions: P at 233, V at 234, A at 235, no residue at 236, G at 327, S at 330 and S at 331 and is at least 98 & identical to a CH2 sequence (residues 231-240) from human IgG1 or IgG2 having said modified amino acids plus a pharmaceutically acceptable carrier for inhibiting monocyte activation, complement mediated lysis and ADDC of target cell in vitro, **does not** reasonably provide enablement for (1) *any* binding molecule which is a recombinant polypeptide comprising

(i) *any* "binding domain" capable of binding to any target molecule and (ii) any effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 32, (2) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) any effector domain is selected from G1Δac or G4Δc as shown in Figure 17, (3) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to *any* target molecule and (ii) any effector domain is selected from G1Δac or G4Δc as shown in Figure 17 "optionally comprising further amino acid substitutions or deletions to render the molecule substantially null allotype, (4) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector chimeric domain wherein the effector domain is derived from any first human immunoglobulin heavy chain CH2 domain wherein at least *any* "1 amino acid" in at least *any* "one region" of the CH2 domain has been modified to the corresponding amino acid from any second, different, human immunoglobulin heavy chain CH2 domain, and wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with *any* first or second human immunoglobulin heavy chain C_H2 domain, (5) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector chimeric domain wherein the effector domain is derived from any first human immunoglobulin heavy chain CH2 domain wherein at least any 1 amino acid in at least any one region of the CH2 domain has been modified to the corresponding amino acid from any second, different, human immunoglobulin heavy chain CH2 domain, and wherein the effector domain has retained an affinity for FcγRIIb, (6) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 32 wherein the binding domain derives from any different source to the effector domain, (7) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 32 wherein the binding domain is capable of binding of any antigen such as the ones recited in claims 38 and 39, (8) any pharmaceutical preparation comprising any binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 32 plus a

pharmaceutically acceptable carrier, (9) *any* binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 41, (10) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and an effector domain wherein the effector domain is selected from G1Δab or G2Δb, (11) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector domain wherein the effector domain is selected from G1Δab or G2Δb "optionally comprising further amino acid substitutions or deletions to render the molecule substantially null allotypic", (12) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector domain wherein the effector domain is derived from any first human immunoglobulin heavy chain CH2 domain wherein at least any one amino acid in at least any one region of the CH2 domain has been modified to the corresponding amino acid from any second, different, human immunoglobulin heavy chain CH2 domain and wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with *any* first or second human immunoglobulin heavy chain C_H2 domain, (13) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector domain wherein the effector domain is derived from any first human immunoglobulin heavy chain CH2 domain wherein at least any one amino acid in at least any one region of the CH2 domain has been modified to the corresponding amino acid from any second, different, human immunoglobulin heavy chain CH2 domain and wherein the effector domain has retained an affinity for FcγRIIb, (14) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector domain wherein the binding domain is derives from a different source from the effector domain, (15) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 41 wherein the binding domain is the ones such as recited in claims 47-48 and (16) *any* pharmaceutical composition comprising any binding molecule as recited in claim 41 plus a pharmaceutical acceptable carrier for treating any disease. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two binding molecules comprising a binding domain selected from the group consisting of CD52 or FOG-1 (RhD antigen on RBC) and an effector domain wherein effector domain is selected from human immunoglobulin IgG1, IgG2 and IgG4 wherein the human IgG1 constant region incorporated IgG2 residues in the region 233-236 and/or IgG4 residues at positions 327, 330 and 331 into the corresponding amino acid residues of IgG1 based on the European Union numbering system. The first region of human IgG1 constant region consisting of residues 233-236, which is part of the hinge link or lower hinge region of the C_H2 domain while the second region 327, 330 and 331 is the N-terminal end of the C_H2 domain. In the effector domain of G1Δab mutation of SEQ ID NO: 1, the E at position 233 of IgG1 is substitute for P from IgG2, the L at position 234 of IgG1 is substitute for V from IgG2, the L at position 235 is substituted for A from IgG2, Since IgG2 has a deletion at 236 where the other class of IgG has G, the mutation at 236 is omitted (no residue) or G, the A at 327 of IgG1 is substitute for G from IgG4, The A at 330 of IgG1 is substitute for S from IgG4 and the P at 331 of IgG1 is substitute for S from IgG4. For the effector domain of G2Δa mutation of SEQ ID NO: 2, E is changed to P at position 233, L to V at position 234, L to A at position 235, a deletion at position 236, A to G at position 327, A to S at position 330 and P to S at position 331. For effector domain of G1Δac mutation of SEQ ID NO: 3, E is changed to P at position 233, L to V at position 234, L to A at position 235, G remains the same at position 236, A to G at position 327, A to S at position 330 and P to S at position 331. The said binding molecules wherein the effector domain selected from the group consisting of SEQ ID NO: 1, 2 and 3 has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1. The said

binding molecules of SEQ ID NO: 1, 2 and 3 wherein the effector domain has retained an affinity for FcγRIIb.

Other than the specific binding molecule mentioned above, the specification does not teach how to make and use *any* binding molecules such as the ones recited in claims 32-49 for a pharmaceutical for treating *any* disease because there is insufficient guidance as to the binding specificity of any undisclosed binding domain within the binding molecule. Further, the term "has" is opened-ended. It expands human immunoglobulin heavy chain CH2 domain to include additional amino acid substitution and deletion in addition to the blocks of amino acids such as the ones recited in claims 32 and 41. There is insufficient guidance as to as to which amino acid within the CH2 domain can be added or deleted in addition to the ones that are already recited in claims 32 and 41, and whether the resulting modification still retain the structure and function such as without triggering significant complement dependent lysis or cell mediated destruction and capable of binding to any of the FcRn and/or FcγRIIb. Given the indefinite number of undisclosed binding molecule, there is insufficient working example to demonstrate that any undisclosed binding molecule is effective for inhibiting complement dependent lysis or cell mediated destruction and capable of binding to any of the FcRn and/or FcγRIIb, much less for treating any disease. Even if the binding molecule wherein the binding domain is limited to CD52 and FOG-1 and the effector domain is limited to SEQ ID NO: 1-3, the specification discloses on page 55 line 46 that "the effect of mutations cannot always be predicted from wildtype antibody activities but will depend on the novel context (based on 'mixed' subclasses of IgG) in which the mutation is present". The specification further discloses that the binding molecule wherein the effector domain such as G1Δb (SEQ ID NO: 1) and G1Δc (SEQ ID NO: 2) have 50 to 10 fold lower complement mediated lysis, respectively, although both G1Δb (SEQ ID NO: 1) and G1Δc (SEQ ID NO: 2) bind to the receptor FcγRII equally (See page 55, last full paragraph).

Mogan *et al* (PTO 1449) teach that changing the Leu235 to Glu in the N-terminal end of the C_H2 domain abolished FcγRI binding and unexpectedly also abolished human complement lysis while the FcγRIII binding is retained (See entire document, page 320, column 1, first paragraph, in particular). Given the lack of guidance as to which amino acid within the effector domain can be mutated in addition to the ones already recited in the claim 32 and the indefinite number of binding domain within the binding molecule, it is unpredictable which undisclosed binding molecule is useful for any purpose, let alone for a pharmaceutical composition for

treating any disease. Since the binding domain of the binding molecule is not enabled, it follows any binding molecule wherein the effector domain such as the ones recited in claim 33 is not enabled. It also follows that any binding molecule wherein effector domain from G1Δb and G1Δc optionally "comprising" further amino acid substitutions or deletions is not enabled. Further, the specification does not define the term "substantially" null allotypic. It also follows that any binding molecule wherein the binding domain derives from a different source to the effector domain is not enabled. It also follows that any binding molecule wherein the binding molecule is capable of binding to any RhD antigen, any HPA alloantigen of platelets, any neutrophil antigen, any T cell receptor, any integrin, any GBM collagen, and Der P1, any HPA-1a, any VAP-1, any laminin, Lutheran, platelet glycoprotein VI, any platelet glycoprotein Ia/IIa is not enable, it also follows that any binding molecule wherein the binding domain such as the ones recited in claims 39 and 47-48 are not enabled.

Although the specification discloses on page 14 allotypic residues are mutated to match those found in other human IgG subclass, the specification does not define which human IgG subclass that the effector domain in the claimed binding molecule has to be matched to, let alone which amino acid within the effector domain of the claimed binding molecule can be modified and still retain its structure and function.

With regard to effector domain in claims 35 and 44, the claims as written fails to indicate which "first human immunoglobulin heavy chain CH2 domain" has been modified to match which "second different human immunoglobulin heavy chain" that would resulted in reduce affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis. Further there is no guidance as to which amino acid within which "region" of the CH2 domain of which undisclosed first human immunoglobulin heavy chain be modified and whether the resulting modified effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis.

With regard to claim 41, there is a lack of guidance as to which amino acid within the CH2 domain can be modified because the term "has" is open-ended. It expands the CH2 domain to include additional modification such as substitution, deletion and addition. Even if the additional modification in CH2 domain is at least 98% identical to a CH2 sequence (residues 231-340) form human IgG1 or IgG2 having said modified amino acids, there is insufficient guidance as to which amino acid within the CH2 of human IgG1 or IgG2 can be modified and that after modification would still retain the structure and function. It is unpredictable which undisclosed

amino acid residue within the CH2 domain could tolerate change. Further, there is a lack of guidance as to the binding specificity of any undisclosed binding domain of any binding molecule, in turn, would be useful for a pharmaceutical preparation for treating any disease.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the lack of guidance and in vivo working examples, predicting what changes can be made to the amino acid sequence in the effector domain of any human immunoglobulin that after insertion and/or modification will retain both structure and have similar function is unpredictable.

Furthermore, it is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular).

Kuby *et al*, of record, teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Riechmann *et al*, of record, teach the effector functions of human IgG3 is less effective in both complement and cell-mediated lysis while IgG2 isotype is weakly lytic and IgG4 is non-lytic (See page 326, Heavy-chain constant domains, in particular). Given the lack of guidance as to the binding specificity of the binding molecule, it is unpredictable which undisclosed binding molecule, which is a recombinant polypeptide, comprising any binding domain capable of binding to any target molecule and any effector domain having extra amino acid substitution, deletion in addition to the ones already in the claims would be useful for treating any disease in the absence of vivo working example.

With regard to pharmaceutical preparation as recited in claims 40 and 49, the specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering any undisclosed binding molecule. The specification disclosed only binding molecule that binds to CD52 and FOG-1. The specification does not teach how to extrapolate data obtained from in vitro binding assays and inhibition of complement mediated cell lysis in vitro to the development of effective in vivo human therapeutic

compositions, commensurate in scope with the claimed invention. Thus it is not clear that the skilled artisan could predict the efficacy of binding molecules exemplified in the specification for treating any disease commensurate in scope encompassed by the claims.

A pharmaceutical preparation in the absence of in vivo data are unpredictable for the following reasons: (1) the binding molecule may be inactivated before producing an effect, i.e. such as proteolytic degradation; (2) the binding molecule may not reach the target area due to metabolic clearance or where the binding molecule has no effect; and (3) other functional properties, known or unknown, may make the binding molecule unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Given the indefinite number of undisclosed binding molecule for treating any disease, the lack of guidance and in vivo working examples, further research is required. For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/6/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims have now been limited to either 233P, 234V, 235A and 236 G or no residue and this clearly excludes all embodiments of Greenwood and Cole et al. (2) The citations refer to by the Examiner do no more than show that some experimentation may be necessary. (3) The table present herewith (Appendix III) makes it clear that the effector domain invention can be practice with different variable regions (all from antibodies) as now required by the claim without the loss of advantages the claimed binding molecule offers since having specified the key residues in the constant region to change to give the improved properties.

In response to Applicant's assertion that claims have now been limited to require either 233P, 234V, 235A and 236 G or no residue, the binding molecule in the amended claims still

have no structure, not to mentioned function because of (1) the lack of binding specificity, (2) the term "has" is opened-ended. It expands human immunoglobulin heavy chain CH2 domain to include additional or "extra" amino acid substitution and deletion in addition to the blocks of amino acids such as the ones recited in claims 32 and 41. There is insufficient guidance as to which amino acid within the CH2 domain can be added or deleted in addition to the ones that are already recited in claims 32 and 41, much less for a pharmaceutical preparation for treating any disease. (3) There is insufficient working example demonstrating that extra modification in the effector domain would still retain both structure and function such as without triggering significant complement dependent lysis or cell mediated destruction and capable of binding to any of the FcRn and/or FcγRIIb. (4) Given the indefinite number of undisclosed binding molecule, there are no in vivo working examples demonstrating that any undisclosed binding molecule is effective for treating any disease. (5) Even if the binding molecule wherein the binding domain is limited to CD52 and FOG-1 and the effector domain is limited to SEQ ID NO: 1-3, there are no in vivo working example that the claimed binding molecules could treat any disease. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

9. Claims 32-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) any effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 32, (2) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) any effector domain is selected from G1Δac or G4Δc as shown in Figure 17, (3) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to *any* target molecule and (ii) any effector domain is selected from G1Δac or G4Δc as shown in Figure 17 "optionally comprising further amino acid substitutions or

deletions to render the molecule substantially null allotype, (4) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector chimeric domain wherein the effector domain is derived from any first human immunoglobulin heavy chain CH2 domain wherein at least *any* "1 amino acid" in at least *any* "one region" of the CH2 domain has been modified to the corresponding amino acid from any second, different, human immunoglobulin heavy chain CH2 domain, and wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with *any* first or second human immunoglobulin heavy chain C_H2 domain, (5) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector chimeric domain wherein the effector domain is derived from any first human immunoglobulin heavy chain CH2 domain wherein at least any 1 amino acid in at least any one region of the CH2 domain has been modified to the corresponding amino acid from any second, different, human immunoglobulin heavy chain CH2 domain, and wherein the effector domain has retained an affinity for FcγRIIb, (6) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 32 wherein the binding domain derives from any different source to the effector domain, (7) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 32 wherein the binding domain is capable of binding of any antigen such as the ones recited in claims 38 and 39, (8) any pharmaceutical preparation comprising any binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 32 plus a pharmaceutically acceptable carrier, (9) *any* binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 41, (10) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and an effector domain wherein the effector domain is selected from G1Δab or G2Δb, (11) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an

effector domain wherein the effector domain is selected from G1Δab or G2Δb "optionally comprising further amino acid substitutions or deletions to render the molecule substantially null allotypic", (12) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector domain wherein the effector domain is derived from any first human immunoglobulin heavy chain CH2 domain wherein at least any one amino acid in at least any one region of the CH2 domain has been modified to the corresponding amino acid from any second, different, human immunoglobulin heavy chain CH2 domain and wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with *any* first or second human immunoglobulin heavy chain C_H2 domain, (13) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector domain wherein the effector domain is derived from any first human immunoglobulin heavy chain CH2 domain wherein at least any one amino acid in at least any one region of the CH2 domain has been modified to the corresponding amino acid from any second, different, human immunoglobulin heavy chain CH2 domain and wherein the effector domain has retained an affinity for FcγRIIb, (14) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) an effector domain wherein the binding domain is derives from a different source from the effector domain, (15) the said binding molecule which is a recombinant polypeptide comprising (i) *any* "binding domain" capable of binding to any target molecule and (ii) effector chimeric domain which "has" the blocks of amino acids at positions as set forth in claim 41 wherein the binding domain is the ones such as recited in claims 47-48 and (16) *any* pharmaceutical composition comprising any binding molecule as recited in claim 41 plus a pharmaceutical acceptable carrier for treating any disease.

The specification discloses only two binding molecules comprising a binding domain selected from the group consisting of CD52 or FOG-1 (RhD antigen on RBC) and an effector domain wherein effector domain is selected from human immunoglobulin IgG1, IgG2 and IgG4 wherein the human IgG1 constant region incorporated IgG2 residues in the region 233-236 and/or IgG4 residues at positions 327, 330 and 331 into the corresponding amino acid residues of IgG1 based on the European Union numbering system. The first region of human IgG1 constant region consisting of residues 233-236, which is part of the hinge link or lower hinge region of the C_H2 domain while the second region 327, 330 and 331 is the N-terminal end of the C_H2 domain. In

the effector domain of G1Δab mutation of SEQ ID NO: 1, the E at position 233 of IgG1 is substitute for P from IgG2, the L at position 234 of IgG1 is substitute for V from IgG2, the L at position 235 is substituted for A from IgG2, Since IgG2 has a deletion at 236 where the other class of IgG has G, the mutation at 236 is omitted (no residue) or G, the A at 327 of IgG1 is substitute for G from IgG4, The A at 330 of IgG1 is substitute for S from IgG4 and the P at 331 of IgG1 is substitute for S from IgG4. For the effector domain of G2Δa mutation of SEQ ID NO: 2, E is changed to P at position 233, L to V at position 234, L to A at position 235, a deletion at position 236, A to G at position 327, A to S at position 330 and P to S at position 331. For effector domain of G1Δac mutation of SEQ ID NO: 3, E is changed to P at position 233, L to V at position 234, L to A at position 235, G remains the same at position 236, A to G at position 327, A to S at position 330 and P to S at position 331. The said binding molecules wherein the effector domain selected from the group consisting of SEQ ID NO: 1, 2 and 3 has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1. The said binding molecules of SEQ ID NO: 1, 2 and 3 wherein the effector domain has retained an affinity for FcγRIIb.

With the exception of the specific binding molecule mentioned above, there is insufficient written description about the structure associated with function of *any* binding molecule because there is inadequate written description about the structure of the binding domain without the amino acid sequence, much less the binding specificity of any binding molecule. Further, the term "has" is opened-ended. It expands human immunoglobulin heavy chain CH2 domain to include additional amino acid substitution and deletion in addition to the blocks of amino acids such as the ones recited in claims 32 and 41. There is inadequate written description about the specific amino acids within the effector domain of the binding molecule can be modified in addition to the stated positions such as the ones recited in claims 32 and 41 or optionally "comprising" further amino acid substitution or deletion to render the undisclosed binding molecule substantially null allotypic. Given the indefinite number of undisclosed binding domain having extra undisclosed modification within the effector domain of any undisclosed binding molecule, the pharmaceutical preparation comprising any undisclosed binding molecule is not adequately described.

Further, the specification discloses only two binding domain such as FOG-1 and anti-CD52 and four specific effector domains such as the ones shown in Figure 17 for in vitro inhibition assays.

Given the lack of a written description of *any* additional representative species of (1) binding domain, and (2) effector domain comprising further amino acid substitution or deletion as encompassed by the claimed binding molecule, much less for a pharmaceutical preparation for treating any disease, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/6/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the sequences of constant regions as well as the variable regions from a variety of species of antibodies are published and known in the art. (2) The specification discloses several example constant regions and narrow genus is claimed based on said constant regions.

In response to Applicant's argument in item (1), the newly added claims are drawn to any binding molecule comprising any binding domain and any effector domain having various modification such as substitution, deletion, addition in addition to the modification stated in positions such as the ones recited in claims 32 and 41. There is insufficient written description about the structure associated with function of *any* binding molecule because there is inadequate written description about the structure of the binding domain without the amino acid sequence, much less the binding specificity of any binding molecule. Further, the term "has" is opened-ended. It expands human immunoglobulin heavy chain CH2 domain to include additional amino acid substitution and deletion in addition to the blocks of amino acids such as the ones recited in claims 32 and 41. There is inadequate written description about the specific amino acids within the effector domain of the binding molecule can be modified in addition to the stated positions such as the ones recited in claims 32 and 41 or optionally "comprising" further amino acid substitution or deletion to render the undisclosed binding molecule substantially null allotypic.

Since the binding molecule mentioned above is not adequately described, any pharmaceutical composition comprising any undisclosed binding molecule for treating any disease is not adequately described. Even if the binding molecule is limited to the specific binding molecule comprising the specific binding domain and the specific effector domain wherein the binding domain is selected from the group consisting of FOG-1 and CAMPATH-1 and the effector domain is selected from the group consisting of SEQ ID NO: 1, SEQ IN NO: 2 and SEQ ID NO: 3, there is inadequate written description about the pharmaceutical preparation for treating any disease.

In response to Applicant's argument in item (2), the specification discloses only the specific binding molecule comprising the specific binding domain and the specific effector domain wherein the binding domain is FOG-1 and CAMPATH-1 and the effector domain selected from the group consisting of SEQ ID NO: 1, SEQ IN NO: 2 and SEQ ID NO: 3 for in vitro screening of the killing of PBMC by complement lysis with CAMMPATH-1 or the killing of RBD by ADCC with Fog-1 associated with fetal thrombocytopenia by way of assessing directly or indirectly through inability to trigger monocyte chemiluminescence. Given the lack of a written description of *any* additional representative species of (1) binding domain, (2) effector domain comprising further amino acid substitution or deletion as encompassed by the claimed binding molecule, and (3) much less for a pharmaceutical preparation for treating any disease, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

10. The following new grounds of objections and rejection are necessitated by the amendment filed 1/6/03.

11. Claim 39 is objected to because "A" should have been "the" for dependent claim.

12. Claim 48 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 39. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

14. Claims 32, 34, 41 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "substantially" in claims 34 and 43 is ambiguous and one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. The specification does not defined what is meant by "substantially". Further, the term "optionally comprising further amino acid substitutions or deletions to render the molecule substantially null allotypic" in claims 34 and 43 now change the scope of the claimed invention. The passage pointed out by Applicant states that "the effector domain comprises an amino acid sequence comprising one or more of the following modifications at the stated positions, numbered with respect to the EU numbering system (Kabat et al) where the position 233 is P, 234V, 235A, 236 either no residue or G, 327G, 330S and 331S.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 32-37, 39-46 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwood *et al* (of record, Eur J Immunol 23: 1098-1104, 1993; PTO 892) in view of Mogan *et al* (of record, Immunology 86: 319-324, 1995, PTO 1449), Chappel *et al* (of record, Proc Nat. Acad. Sci. USA 88: 9036-40, 1991; PTO 1449) and Cole *et al* (of record, Immunology 159: 3613-21, 1997; PTO 1449).

Greenwood *et al* teach a binding molecule such as chimeric recombinant antibodies DS1141 and DS4414 comprising (i) a binding domain capable of binding a target molecule such as CAMPATH-1 antigen (CD52) and (ii) an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human immunoglobulin heavy chain wherein the reference binding molecule is capable of binding to the target molecule without significant complement mediated lysis or triggering cell mediated destruction of the target (ADCC) and the reference chimeric effector domain is derived from human immunoglobulin heavy chain CH2 domain from IgG1, and IgG4 (See Figs 1-4, in particular). Greenwood *et al* teach that the structural requirements for effector function are located in the C-terminal half of the CH2 domain (residues 234, 238 and the hinge-link region from 300-331 (See page 1103, Fig 5, in particular). Greenwood *et al* teach that the four residues could be responsible for the failure or lack of ADCC are Tyr at 296 in IgG1 vs. Phe in IgG4, Ala in 327 versus Gly in IgG4, Ala in 330 in IgG1 versus Ser in IgG4 and Pro at 331 in IgG1 to Ser in IgG4 (See Fig 5, page 1104, column 1, first full paragraph, in particular). The reference binding molecule wherein the first human immunoglobulin is IgG1 and the second human immunoglobulin is IgG4 (See Fig 1, in particular). The reference binding molecule wherein 2 amino acids in 1 region such as the C terminal half of the C_H2 domain are modified to the corresponding amino acids from a second human immunoglobulin heavy C_H2 domain such as IgG4 (See Fig 5, in particular). The reference binding molecule wherein the effector domain shares at least about 98% identity with the wild type human immunoglobulin heavy chain CH2 domain since it has only one, two or maximum four mutations in the C_H2 domain compared with the wild type. The reference binding molecule comprises a human immunoglobulin heavy chain C_H2 domain having A at position 235, G at position 327, S at positions 330 and 331(See Figs 1 and 5, in particular). The reference binding molecule comprises a human immunoglobulin heavy chain CH2 domain having a block of amino acids such as G position 327, S at positions 330 and 331. (See Figs 1 and 5, in particular). The reference binding molecule wherein the binding domain is derived from a different source such as rat or chimeric humanized CAMPATH-1 antibodies to the effector domain (See page 1099,

Materials and methods, in particular). The reference binding molecule is an antibody wherein the binding domain is capable of binding to a glycoprotein such as CAMPATH-1 (CD52) (See page 1099, Materials and methods, Introduction in particular). Greenwood *et al* further teach a pharmaceutical acceptable carrier such as IMDM for a pharmaceutical preparation comprising the reference binding molecule (See page 1099, column 2, ADCC, in particular). Greenwood *et al* teach IgG1 is the most potent isotype in ADCC, with IgG3 somewhat less effective and IgG2 and IgG4 ineffective. The residues in the hinge-link region (233-238) are crucial to binding to the high affinity receptor FcγRI and the binding site for FcγRIII is overlapping this region (See page 1099, column 1, first paragraph, in particular). Greenwood *et al* teach it is possible to improve the antibody effector functions of any antibody by construction of novel antibodies that either possess ADCC or complement mediated killing or the lack thereof for therapy such as donor heterogeneity having the reference modified amino acid residues (See abstract, page 1099, column 1, second paragraph, in particular).

The claimed invention as recited in claim 32 differs from the teachings of the reference only that the binding molecular wherein the CH2 effector domain has the 233P, 234V, and 236G.

The claimed invention as recited in claim 33 differs from the teachings of the reference only that the binding molecular wherein the CH2 effector domain G1Δac having the specified amino acids at positions (223P, 234V, 235A, 236G, 327G, 330S, and 331S) and G4Δc (233P, 234V, 235A, 236G, 327G, 330S and 331S).

The claimed invention as recited in claim 34 differs from the teachings of the reference only that the binding molecular wherein the CH2 effector domain G1Δac has the specified amino acids at positions (223P, 234V, 235A, 236G, 327G, 330S, and 331S) and G4Δc (233P, 234V, 235A, 236G, 327G, 330S and 331S) optionally further comprising amino acid substitutions, or deletions to render the molecule substantially null allotypic.

The claimed invention as recited in claim 41 differs from the teachings of the reference only that the binding molecular wherein the CH2 effector domain has the following blocks of amino acids at the stated positions: 233P, 234V, 235A, no residue at 236, 237G, 330S, and 331S and is at least 98% identical to a CH2 sequence (residues 231-240) from human IgG1, or IgG2 having said modified amino acids.

The claimed invention as recited in claim 42 differs from the teachings of the reference only that the binding molecular wherein the effector domain is G1Δab (233P, 234V, 235A, 236G, 327G, 330S and 331S) or G2Δa (233P, 234V, 235A, no residue at 236, 327G, 330S, and 331S).

The claimed invention as recited in claim 43 differs from the teachings of the reference only that the binding molecular wherein the effector domain is G1Δab (233P, 234V, 235A, 236G, 327G, 330S and 331S) or G2Δa (233P, 234V, 235A, no residue at 236, 327G, 330S, and 331S) optionally comprising further amino acid substitutions or deletions to render the molecule substantially null allotypic.

The claimed invention as recited in claim 44 differs from the teachings of the reference only that the binding molecule wherein the effector domain has reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1.

Mogan *et al* (PTO 1449) teach a binding molecule such as G1 [L235A] which is a recombinant polypeptide such as recombinant immunoglobulin comprising (i) a binding domain capable of binding a target molecule such as HLA-DR and (ii) an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human immunoglobulin heavy chain wherein the reference binding molecule is capable of binding to the target molecule without triggering significant complement dependent lysis or cell mediated destruction of the target (Table 2, page 321, in particular). The reference chimeric effector domain having Leu at position 235 in the C_H2 domain of IgG1 changes to Ala (A) taken from IgG2; the reference effector domain is still capable of binding to FcRn such as FcγRI but the binding is reduced by about 100-fold. The reference teaches that changing Leu at position 235 to Glu in human IgG4 abolished complement lysis (no killing of target) while Ala at 235 permitted low levels of killing (See page 322, column 1, last paragraph, bridging column 2, in particular).

Chappel *et al* (of record, 1449) teach a binding molecule which is a recombinant polypeptide such as recombinant immunoglobulin comprising (i) a binding domain capable of binding a target molecule such as dinitrophenyl and (ii) an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human immunoglobulin heavy chain wherein the reference binding molecule is capable of binding to the target molecule and the reference chimeric effector domain is derived from human immunoglobulin heavy chain C_H2 domain selected from IgG1, IgG2 and IgG4 wherein 2 amino acids in region 231-238 of the C_H2 domain have been modified such as substitution and/or deletion to the corresponding amino acids from a different human immunoglobulin heavy chain C_H2 domain such as IgG2 and IgG4 (See Materials and Methods, Table 2, in particular). The reference human immunoglobulin is selected from IgG1, IgG2 and IgG4 (See Table 2, in particular). The reference binding molecule

such as IgG2-2-1 hybrid immunoglobulin binds to the FcγRI on U937 cells (See page 9038, column 1, in particular). The reference binding molecule has progressive substitution such as two, three or four amino acids in 1 region such as 231-238 of the C_H2 domain of IgG1, IgG2 or IgG4 for to the corresponding amino acids from a second (wild type) human immunoglobulin heavy chain C_H2 domain (See page 9039, Table 2, column 1, Table 4, in particular). The reference binding molecule wherein the effector domain shares at least 98% identity with the wild type human immunoglobulin heavy chain CH2 domain since it has only one, two or maximum four mutations in the CH2 domain compared with the wild type. The reference binding molecule comprises a human immunoglobulin heavy chain CH2 domain having one or more amino acids substitution from E to P at position 233, L to V at position 234, L to A at position 235, no residue or glycine at position 236 in accordance with the EU numbering system (See page 9038, column 2, in particular). The reference binding molecule wherein the binding domain is the binding site of an antibody (See page 3097, column 1, in particular). Chappel *et al* teach that reciprocal shuffling of the C_H2 domains between IgG1 and IgG2 subclass unambiguously revealed that the FcγRI binding is located in the C_H2 domain and effector function can be abolish in all IgG1 containing IgG C_H2 domain (See page 9039, column 2, last paragraph, in particular).

Cole *et al* (of record, Immunology 159: 3613-3621; PTO 1449) teach a binding molecule which is a recombinant polypeptide comprising a binding domain capable of binding to a target molecule such as a T cell receptor and an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human heavy chain wherein the effector domain comprises a human immunoglobulin heavy chain of IgG2 having at least 2 amino acids at position 234 and 235 have been modified to V and A, respectively (See page 3615, Table 1, in particular). The said effector domain is capable of specifically binding to FcγIIb, and is derived from two or more human immunoglobulin heavy chain C_H2 domains from IgG2 (See page 3614, Materials and Methods, page 3617-3619, in particular). Cole *et al* teach that binding molecule such as anti-CD3 having Ala at 234, Ala or Glu at 235, Gly or no residue at 236 in the CH2 effector domain of CH2 has low affinity for FcγRI and FcγRII, and is ineffective in mediating cytotoxicity against target cells (See Table 1, page 3617, column 2, page 3620, column 1, in particular). The reference amino acid substitution in the particular residues within the CH2 effector domain of human IgG2 is useful for retaining potent immunosuppressive properties (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine or substitute the human immunoglobulin heavy chain C_H2 domain of the IgG1 within the binding molecule as taught by Greenwood *et al* for the specified amino acid at the specified position such as the A at position 235, and Glu at position 235 as taught by Mogan *et al* or the P at position 233, V at position 234, A at position 235, no residue or glycine at position 236 in accordance with the EU numbering system as taught by Chappel *et al* or the V at position 234 and A at position 235 as taught by Cole *et al* for a binding molecule comprising any binding domain and an effector domain from human immunoglobulin heavy chain having (P at position 233, V at 234, A at 235, G at 236, G327, S330 and 331) or (P at 233, V at 234, A at 235, no residue at 236, G at 327, S at 330, and S at 331) as taught by the Greenwood *et al,* Mogan *et al,* Chappel *et al* and Cole *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Mogan *et al* teach that Ala at 235 permitted low levels of killing (See page 322, column 1, last paragraph, bridging column 2, in particular). Chappel *et al* teach reciprocal shuffling of the C_H2 domains between IgG1 and IgG2 subclass and having one or more amino acids substitution such as from P at position 233, V at position 234, A at position 235, no residue or glycine at position 236 in accordance with the EU numbering system can abolish effector function in the all IgG1 containing IgG C_H2 domain (See page 9039, column 2, last paragraph, in particular). Cole *et al* teach that IgG2 variant having Ala at 234, Ala or Glu at 235, Gly or no residue at 236 have low affinity for FcγRI and FcγRII, and they are ineffective in mediating cytotoxicity against target cells (See page 3617, column 2, page 3620, column 1, in particular). Greenwood *et al* teach it is possible to improve the antibody effector functions of any antibody by construction of novel antibodies that either possess ADCC or complement mediated killing or the lack thereof for therapy such as donor heterogeneity (See abstract, page 1099, column 1, second paragraph, in particular).

Applicants' arguments filed 1/6/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Greenwood et al teach DS111/41 and DS444/14 mutants have modified CH2 regions. It can be inferred from the citation that neither of these have the sequence required by the amended claims i.e. 233P, 234V, 235A and 236 (G or deleted) and

327G, 330S and 331S. Green et al include several changes that are irrelevant to the present invention (274, 296, 300, 309 and 339). None of the mutants taught by Greenwood et al improve over IgG4 in respect to ADCC. The 233-236 residues are an important factor in ADCC, which is not taught, or suggest by Greenwood et al. Greenwood et al does not teach the desirability of balancing of these other functions (FcRn and/or FcyRIIb), the mutations would achieved the desired functions, or whether making "extra" mutations would negate or affect the ADCC and lysis function. (2) None of the cited references would have suggested the combination of residues now specified in the claims. (3) Morgan et al with C1q, FcyRI, and FcyRIII binding and is not concerned with other effector functions required by the claims (minimizing ADCC). The reference does not teach the desirability of balancing of these other functions (FcRn and/or FcyRIIb), the mutations would achieved the desired functions, or whether making "extra" mutations would negate or affect the ADCC and lysis function. (4) Chappel et al correctly focused attention on the lower hinge region of the CH2 domain. Unlike the present invention, Chappel et al was concerned only with the high affinity receptor FcyRI and not the low affinity receptor. (5) Cole et al's V234 and A23A are native IgG2 and Cole et al have not shown to bind FcRn and/or FcyRIIb.

In response to Applicant's arguments, Greenwood *et al* teach that it is possible to improve the antibody effector functions of any antibody by construction of novel antibodies that either possess ADCC or complement mediated killing or the lack thereof for therapy such as donor heterogeneity (See abstract, page 1099, column 1, second paragraph, in particular).

Greenwood *et al* teach substituting A at 325 (325A), G at 327 (327G), S at 330 and 331 (330S, and 331S) in the human CH2 domain of IgG1 or IgG 4. While Greenwood et al do not teach 233P, 234V, 235A and 236 (G or deleted) and 327G, 330S and 331S, Mogan *et al* teach substitution A at 325 in human IgG1. Chappel *et al* teach substituting P at position 233, V at position 234 and A at position 235 in CH2 domain of IgG1, IgG2 and IgG4 and Cole *et al* teach IgG2 variants having Ala at 234, Ala or Glu at 235, Gly or no residue at 236 has low affinity for FcγRI and FcγRII, and is ineffective in mediating cytotoxicity against target cells (See Table 1, page 3617, column 2, page 3620, column 1, in particular). From the combined teachings of Greenwood *et al,* Mogan *et al* Cole *et al* and Chappel *et al,* it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention. Further, the term "has" in amended claims 32 and 41 is open-ended. It expands CH2 domain to include additional amino acid substitutions to read on the teachings of Greenwood et al. In response to

Applicant's argument that none of the references teach the desirability of balancing of these other functions (FcRn and/or FcγRIIb), it is noted that base claims 32 and 41 recite FcRn and Fc; FcRn or FcγRIIb.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). The strongest rationale for combining references is a recognition in the art that some advantage or expected beneficial result such as reduce ADCC or complement mediated lysis would have been produced by their combination. This recognition may be an expressed statement in a reference, an implication that can be drawn from one or more references or a convincing line or reasoning based upon established principles or legal precedent. In this case, Greenwood *et al* teach that IgG1 is the most potent isotype in ADCC, with IgG3 somewhat less effective and IgG2 and IgG4 are ineffective. The residues in the hinge-link region (233-238) are crucial to binding to the high affinity receptor FcγRI and the binding site for FcγRIII is overlapping this region (See page 1099, column 1, first paragraph, in particular). Greenwood *et al* teach that it is possible to improve the antibody effector functions of any antibody by construction of novel antibodies that either possess ADCC or complement mediated killing or the lack thereof for therapy such as donor heterogeneity (See abstract, page 1099, column 1, second paragraph, in particular). Mogan *et al* (PTO 1449) teach that a chimeric effector domain having Leu at position 235 in the C_H2 domain of IgG1 changes to Ala (A) taken from IgG2 still capable of binding to FcRn such as FcγRI but the binding is reduced by about 100 fold. The reference teaches changing Leu at position 235 to Glu change in human IgG4 abolished complement lysis (no killing of target) while Ala at 235 permitted low levels of killing (See page 322, column 1, last paragraph, bridging column 2, in particular).

Chappel *et al* teach that FcγRI binding is located in the C_H2 domain and effector function which can be abolish in all IgG1 containing IgG C_H2 domain (See page 9039, column 2, last paragraph, in particular) having one or more amino acids substitution from E to P at position 233,

L to V at position 234, L to A at position 235, no residue or glycine at position 236 in accordance with the EU numbering system (See page 9038, column 2, in particular).

Cole et al teach that effector function such as binding to FcγIIb is within the 234-236 region of the constant CH2 domain of human immunoglobulin IgG2; amino acid substitution such as Ala at 234, Ala or Glu at 235, Gly or no residue at 236 resulted in low affinity for FcγRI and FcγRII, and is ineffective in mediating cytotoxicity against target cells (See Table 1, page 3617, column 2, page 3620, column 1, in particular).

18. Claims 34 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwood *et al* (of record, Eur J Immunol 23: 1098-1104, 1993; PTO 892) in view of Mogan *et al* (of record, Immunology 86: 319-324, 1995, PTO 1449), Chappel *et al* (of record, Proc Nat. Acad. Sci. USA 88: 9036-40, 1991; PTO 1449) and Cole *et al* (of record, Immunology 159: 3613-21, 1997; PTO 1449) as applied to claims 32-37, 39-46 and 49 mentioned above and further in view of WO 95/05468 publication (of record, Feb 1995, PTO 892).

The combined teachings of Greenwood *et al,* Morgen *et al*, Chappel *et al*, and Cole *et al* have been discussed supra.

The claimed invention as recited in claim 34 differs from the teachings of the reference only that the binding molecular wherein the CH2 effector domain G1Δac having the specified amino acids at positions (223P, 234V, 235A, 236G, 327G, 330S, and 331S) and G4Δc (233P, 234V, 235A, 236G, 327G, 330S and 331S) further comprising amino acid substitutions, or deletions to render the molecule substantially null allotypic.

The claimed invention as recited in claim 43 differs from the teachings of the reference only that the binding molecular wherein the effector domain is G1Δab (233P, 234V, 235A, 236G, 327G, 330S and 331S) or G2Δa (233P, 234V, 235A, no residue at 236, 327G, 330S, and 331S) comprising further amino acid substitutions or deletions to render the molecule substantially null allotypic.

The WO 95/05468 publication teaches binding molecule such as CAMPATH-1 recombinant antibodies which has a first amino acid sequence comprising a domain with an ability to bind to a target and a second amino acid sequence comprising part or all of a human immunoglobulin heavy chain having an allotypic determinant associated with a desired effector function (See abstract, in particular). The WO 95/05468 publication teaches aglycosylated mutation having Asn changes to Ala at position 297 of the human IgG1 domain; the mutant

having Ala at position 297 abolishes N-linked glycosylation and fails to mediate complement lysis (See page 12, line 14-17, page 17, line 16-19, page 18, lines 22-25, page 19, lines 20-22, in particular). The WO 95/05468 publication further teaches allotypic polymorphism is to a certain extend responsible for different effector functions and one can moderate the functions of one subclass by introducing mutations at positions homologous to given alleles of another subclass, then the activity in complement activation of the mutant should be reduced compared to the wild type (See page 28, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the amino acid substitution such as Asn at position 297 for Ala in the CH2 domain of human IgG1 domain to abolish N-linked glycosylation or to introduce additional amino acid substitution mutations at positions homologous to a given alleles of another subclass to achieve the desired effector function as taught by the WO 95/05468 publication for a binding molecule comprising a binding domain that binds to CD52 and effector domain that has A at position 235, G position 327, S at position 330 and 331 as taught by Grenwood *et al*, A at 235 as taught by Morgan, 233P, 234V, 235V, no residue at 236 as taught by Chappel et al and 234V, 235A and G or no residue at 236 as taught by Cole et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 95/05468 publication teaches allotypic polymorphism is to a certain extend responsible for different effector functions and one can moderate the functions of one subclass by introducing mutations at positions homologous to given alleles of another subclass, then the activity in complement activation of the mutant should be reduced compared to the wild type (See page 28, in particular) and further mutation by site-directed mutagenesis in any C_H2 domain would render the molecule substantially null allotypic.

Applicants' arguments filed 1/6/03 have been fully considered but are not found persuasive.

Applicants' position is that the rejection is moot since the relevant claims depend from claims which are novel and inventive.

However, the claims are not much differ from those described in the combined references. In the absence of unexpected results, applicant's arguments were not found persuasive.

19. Claims 38-39 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwood *et al* (of record, Eur J Immunol 23: 1098-1104, 1993; PTO 892) in view of Mogan *et al* (of record, Immunology 86: 319-324, 1995, PTO 1449), Chappel *et al* (of record, Proc Nat. Acad. Sci. USA 88: 9036-40, 1991; PTO 1449) and Cole *et al* (of record, Immunology 159: 3613-21, 1997; PTO 1449) as applied to claims 32-37, 39-46 and 49 mentioned above and further in view of US Pat No 5,831,063 (of record, Nov 1998, PTO 892).

The combined teachings of Greenwood *et al,* Morgen *et al*, Chappel *et al*, and Cole *et al* have been discussed supra.

The claimed invention as recited in claims 38 and 47 differs from the teachings of the references only by the recitation that the binding domain is capable of binding to the RhD antigen of red blood cells.

The claimed invention as recited in claims 39 and 48 differs from the teachings of the references only by the recitation that the binding domain is FOG1.

The '063 patent teaches recombinant human monoclonal anti-Rh(D) antibodies and a method of making said antibody that binds to antigen such as FOG1 on human red blood cell (See abstract, column 2, line 41, in particular). The '063 patent teaches the reference antibody is useful for both therapy for passive immunization to prevent hemolytic disease of the newborn and diagnosis (column 4, lines 14-23, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the binding domain of CAMPATH-1 as taught by Greenwood *et al* for the binding domain of FOG-1 as taught by the '063 patent for a binding molecule which is a recombinant polypeptide comprising a binding domain capable of binding to FOG-1, which is the RhD antigen on red blood cell, and an effector domain having an amino acid sequence substantially homologous to all or part of the a constant domain of a human immunoglobulin heavy chain as taught by Greenwood *et al,* Morgen *et al*, Chappel *et al*, and Cole *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '063 patent teaches the antibody is useful for both therapy for passive immunization to prevent hemolytic disease of the newborn and diagnosis (column 4, lines 14-23, in particular).

Applicants' arguments filed 1/6/03 have been fully considered but are not found persuasive.

Applicants' position is that the rejection is moot since the relevant claims depend from claims which are novel and inventive.

However, the claims are not much differ from those described in the combined references. In the absence of unexpected results, applicant's arguments were not found persuasive.

20. No claim is allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

23. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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March 24, 2003

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